Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-16 are sought to be amended. Upon entry of the foregoing amendment, claims 1-16 are pending in the application, with claim 1 being the independent claim. Claims 1-16 have been amended merely to correct obvious typographical errors. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Objection to the Claims

The Examiner objected to claims 1-12 because of various informalities. In particular, the Examiner objected to claim 1 for recitation of the language "comprising by a combination." (*See* Office Action, page 2.) Applicants have amended claim 1 to remove the objected to language, thereby rendering this objection moot.

The Examiner also asserted that claims 1-12 state steps which are recited as either x) or (x) and suggested that "since claim 1 recites (x), that all of the proceeding claims also follow this format." (Office Action, page 3.) In accordance with the Examiner's suggestion, the claims have been amended to follow the "(x)" format, thereby rendering this objection moot.

Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claim 6 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. (*See* Office Action, page 3.) Specifically, the Examiner asserted that the term "employed" lacked antecedent basis. Applicants have deleted this term from claim 6, thereby obviating the rejection.

Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 1 and 3-12 under 35 U.S.C. § 112, first paragraph, because

> [t]he specification, while being enabling for a method of purifying recombinant human erythropoietin from cell culture supernatants comprising recombinant erythropoietin by the method of claim 2, does not reasonable provide enablement for a method for purifying recombinant human erythropoietin from any cell culture supernatant via any combination of the claimed purification steps.

(Office Action, page 4.) Applicants respectfully disagree with the Examiner's assertion and traverse this rejection.

On page 6 of the Office Action, the Examiner asserts that "[t]he skilled artisan would understand that purification of EPO is unpredictable, and that protein purification as a whole requires difficult and tedious experimentation." While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, in *In re Angstadt*, the Court of Custom and Patent Appeals has specifically cautioned that the

unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

537 F.2d at 503, 190 USPQ at 219 (emphasis in the original).

"[U]npredictability [in the art may] . . . be enough to create reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim, [t]his will be . . . the case where the statement is, on its face, *contrary* to generally accepted scientific principles." *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971) (emphasis added). However, this is clearly not the case with the present application. There are no statements in the specification that were contrary to generally accepted scientific principles at the time the application was filed. In addition, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

With regard to the Examiner's statement that yeast cell cultures would not contain erythropoietin, the claims are drawn to erythropoietin purification from cell supernatants that contain erythropoietin. One of ordinary skill in the art would know which cell cultures produce erythropoietin and which do not. There is no undue experimentation necessary in testing for the presence of a specified protein.

Furthermore, the attached Declaration of Dr. Marcelo E. Criscuolo (Exhibit A) describes an additional experiment showing that the purification of human EPO may be performed using a protocol comprising the steps as described in the specification, wherein the purification steps are performed in variable order. The purification results of the human EPO described in the attached experiment is comparable to that of the Examples of the instant specification. As demonstrated by the attached Declaration, one of skill in the art, in view of the guidance provided in the specification and the knowledge of the art, could purify erythropoietin according to, and commensurate in scope with the claimed invention without undue experimentation.

Applicants note that enablement is determined as of the application's filing date. However, a post-filing date declaration setting forth test results substantiating enablement of the claimed invention "pertains to the accuracy of a statement already in the specification. . . . It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)." *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995).

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 13-16 under 35 U.S.C. § 102(b) as allegedly being anticipated by Rosen (International Publication No. WO 92/06116). (*See* Office Action, page 8.)

Anticipation of a claim under § 102 can be found only if the prior art reference discloses each and every element as set forth in the claim. *See Glaxo Inc. v. Novopharm Ltd.*, 34 U.S.P.Q.2d 1565, 1567 (Fed. Cir. 1995), *cert denied,* 116 S. Ct. 516 (1995). Further, "[a]n anticipating reference must describe the . . . [claimed] subject matter with

sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention." *ATD Corp. v. Lydall Inc.*, 48 U.S.P.Q.2d 1321, 1328 (Fed. Cir. 1998). Therefore, in order for the Rosen reference to anticipate the claimed invention, it must describe each and every limitation of Applicants' claimed invention such that the subject matter would be recognized by one skilled in the art.

The claimed invention is directed to a substantially pure erythropoietin produced by a method comprising a combination of the steps of differential saline precipitation; hydrophobic interaction chromatography; concentration and diafiltration; anionic exchange chromatography; cationic exchange chromatography; concentration and diafiltration; and molecular exclusion chromatography. Applicants submit that Rosen does *not* describe a substantially pure erythropoietin prepared by such a method.

Rosen describes the production of hybrid growth factors comprising the amino acid sequence of two different individual growth factors, one of these individual growth factors being human erythropoietin, *i.e.* fusion proteins. Furthermore, Rosen does not describe any purification methods for such fusion proteins. Moreover, Rosen does not teach the same erythropoietin protein sequence; there is an additional amino acid at position 166. In contrast to Rosen, the present invention relates to a purified erythropoietin molecule with 165 amino acids. Therefore, the proteins are different.

With regard to the Examiner's statement that the patentability of a product does not depend upon its method of production, that proposition is only sound if the products are identical. Erythropoietin is a glycoprotein which comprises a polypeptide backbone to which four oligosaccharide motifs are attached in well-specified positions. These oligosaccharides are responsible for the mean life of the protein, and therefore for the

biological effect of the protein as well. The post-translation process responsible for the glycosylation is dependent upon the cell synthesizing the protein and physiological conditions. *See* Rambach *et al.*, *Proceedings of the Society for Experimental Biology and Medicine* 99: 482-483 (1958); Lowy *et al.*, *Nature* 185: 102-103 (1960); Lukowsky *et al.*, *Canadian Journal of Biochemistry* 50: 909-917 (1972); Goldwasser *et al.*, *Journal of Biological Chemistry* 249: 4202-4206 (1974). As a consequence of this phenomenon, erythropoietin exists as a mixture of variants which differ in glycosylation patterns, despite the fact that they are homogeneous with regard to their amino acid sequence. *See* Rademacher *et al.*, *Annual Review of Biochemistry* 57: 785-838 (1998); Cumming, D.A. *Glycobiology* 1: 115-130 (1991); Storring, P.L. *Trends in Biotechnology* 10: 427-432 (1992); Sasaki *et al.*, *Journal of Biological Chemistry* 262: 12059-12076 (1987); Takeuchi *et al.*, *Journal of Biological Chemistry* 263: 3657-3663 (1988); Sasaki *et al.*, *Biochemistry* 27, 8618-8626 (1988); Watson *et al.*, *Glycobiology* 4: 227-237 (1994) Rice *et al.*, *Analytical Biochemistry* 206: 278-287 (1992); Storring *et al.*, *British Journal of Haematology* 100: 79-89 (1998). Moreover, the purification of a glycoprotein may result in different preparations with regard to the different isoforms of the protein, which can be influenced by the selectivity of the procedural steps employed in its purification. *See* Storring *et al.*, *Acta Endocrinologica* 101: 339-347 (1982).

In view of the above, it is very difficult to define the erythropoietin product but through its method of production and purification which determine the characteristics of the product. Since Rosen's product is a fusion protein containing only a portion of the erythropoietin molecule, since Rosen's erythropoietin amino acid sequence is different from that of Applicants' erythropoietin sequence, and since the glycosylation pattern of different erythropoietin preparations vary, the method of production can indeed impart

patentability upon this erythropoietin product. Since Rosen clearly does not teach a substantially pure erythropoietin molecule purified by the claimed purification steps, it is clear that the present invention cannot be anticipated by the Rosen reference.

Allowable Subject Matter

The Examiner objected to claim 2 as being dependent on a rejected base claim, but asserted that it would be allowable if rewritten in independent form. (*See* Office Action, page 10.) Applicants thank the Examiner for pointing out allowable subject matter. However, since it is Applicants' position that claim 1 is allowable, it is also Applicants' position that claim 2, as written, is likewise allowable.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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